EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA); Scientific Opinion on the substantiation of health claims related to soy isoflavones and maintenance of bone mineral density (ID 1655) and reduction of vasomotor symptoms associated with menopause (ID 1654, 1704, 2140, 3093, 3154, 3590) (further assessment) pursuant to Article 13(1) of Regulation (EC) No 1924/2006

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SCIENTIFIC OPINION

Scientific Opinion on the substantiation of health claims related to soy isoflavones and maintenance of bone mineral density (ID 1655) and reduction of vasomotor symptoms associated with menopause (ID 1654, 1704, 2140, 3093, 3154, 3590) (further assessment) pursuant to Article 13(1) of Regulation (EC) No 1924/2006[1]

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)[2, 3]

European Food Safety Authority (EFSA), Parma, Italy

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ABSTRACT

Following a request from the European Commission, the Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to provide a scientific opinion on health claims pursuant to Article 13 of Regulation (EC) No 1924/2006 in the framework of further assessment related to soy isoflavones and maintenance of bone mineral density and reduction of vasomotor symptoms associated with menopause. The food constituent that is the subject of the claim, soy isoflavones, is sufficiently characterised. The claimed effects, maintenance of bone mineral density and reduction of vasomotor symptoms associated with menopause, which are eligible for further assessment, are beneficial physiological effects. The proposed target populations are peri- and/or post-menopausal women. On the basis of the data presented, the Panel concludes that the evidence provided is insufficient to establish a cause and effect relationship between the consumption of soy isoflavones and maintenance of bone mineral density, and between the consumption of soy isoflavones and reduction of vasomotor symptoms associated with menopause.

KEY WORDS

Soy isoflavones, bone mineral density, vasomotor symptoms, menopause, health claims.

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[1] On request from the European Commission, Question No EFSA-Q-2012-00165, EFSA-Q-2012-00166, EFSA-Q-2012-00167, EFSA-Q-2012-00170, EFSA-Q-2012-00212, EFSA-Q-2012-00213, EFSA-Q-2012-00214, adopted on 27 June 2012.

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[3] Acknowledgement: The Panel wishes to thank the members of the Working Group on Claims for the preparatory work on this scientific opinion: Carlo Agostoni, Jean-Louis Bresson, Susan Fairweather-Tait, Albert Flynn, Ines Golly, Marina Heinonen, Hannu Korhonen, Martinus Løvik, Ambroise Martin, Hildegard Przyrembel, Seppo Salminen, Yolanda Sanz, Sean (J.J.) Strain, Inge Tetens, Hendrik van Loveren and Hans Verhagen.

[4] Appendix B was missing from the original publication and has been added to this output.

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SUMMARY

Following a request from the European Commission, the Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to provide a scientific opinion on a list of health claims pursuant to Article 13 of Regulation (EC) No 1924/2006. The Commission has agreed with EU Member States that a certain number of Article 13 health claims would be eligible for further assessment by EFSA in order to be able to take a final decision on whether or not to include these claims in the list of permitted health claims. This opinion addresses the scientific substantiation of a health claim in relation to soy isoflavones and maintenance of bone mineral density and reduction of vasomotor symptoms during menopause. The assessment is based on the information provided by the Member States in the consolidated list of Article 13 health claims, references that EFSA has received from Member States or directly from stakeholders and the additional information provided by the competent Authorities of Germany and Austria for the further assessment of these claims.

The food constituent that is the subject of the health claims is soy isoflavones. The Panel considers that soy isoflavones are sufficiently characterised.

Maintenance of bone mineral density

The claimed effect which is eligible for further assessment relates to the maintenance of bone mineral density. The proposed target population is post-menopausal women. The Panel considers that maintenance of bone mineral density is a beneficial physiological effect.

Among the 14 studies provided which addressed the effects of soy isoflavones on bone mineral density at different bone sites in post-menopausal women, only two by the same research group reported an effect of soy isoflavones at doses of 54 mg/day at the lumbar spine and femoral neck, which was accompanied by a significant increase in markers of bone formation and a significant decrease in markers of bone resorption. Both studies were performed in early post-menopausal women with osteopenia or osteoporosis. The remaining 12 studies used doses of isoflavones up to 200 mg/day and showed no effect of soy isoflavones on bone mineral density. None of these 12 studies reported an effect of soy isoflavones on markers of bone formation or resorption. The Panel notes that five of these studies may have been underpowered to detect an effect of the intervention on bone, whereas in seven studies the number of subjects per intervention arm completing the study ranged between approximately 50 and 120.

Among the five human intervention studies which allowed conclusions to be drawn on the effects of soy isoflavones administered for 6-9 months on bone mineral density in peri/post-menopausal women, one showed a beneficial dose-response effect on bone mineral density at the lumbar spine and femoral neck at doses of 84 and 126 mg/day which may have been associated with a transient decrease in bone resorption, two studies reported a beneficial effect of 80 mg/day and 90 mg/day soy isoflavones on bone mineral density at the lumbar spine with no effect on markers of bone turnover, and two studies using doses of soy isoflavones of 91 mg/day, and 52 and 96 mg/day, one of which reported a significant decrease in markers of bone formation and resorption in the soy isoflavone group, showed no effect of soy isoflavones on bone mineral density at any site.

The Panel notes the exploratory nature and small sample size of these studies. However, the Panel considers that they provide some evidence for an effect of soy isoflavones on the attenuation of bone mineral density loss at the lumbar spine in post-menopausal women when consumed for 6-9 months, possibly mediated by a decrease in bone resorption. The Panel also notes that such changes in BMD at the lumbar spine may result from a change in the remodelling balance which may not be retained in subsequent remodelling cycles (i.e. the remodelling transient).

In weighing the evidence the Panel took into account that of 14 studies lasting ≥12 months, two studies, one of which had 30 subjects per intervention arm, showed an effect of soy isoflavones on bone mineral density at doses of 54 mg/day, whereas 12, seven of which had a sample size per study arm of at least 50 subjects, did not show an effect at doses of 40 to 200 mg/day. The Panel also took into account that these inconsistent findings cannot be explained by differences in study size, dose of

soy isoflavones used, duration of the intervention, or post-menopausal status, that the changes in bone mineral density at the lumbar spine observed in some short-term studies (six to nine months) may result from a change in the remodelling balance which may not be retained in subsequent remodelling cycles (i.e. the remodelling transient), and that the evidence for a mechanism by which soy isoflavones may exert an effect on bone mass and turnover in post-menopausal women is weak.

On the basis of the data presented, the Panel concludes that the evidence provided is insufficient to establish a cause and effect relationship between the consumption of soy isoflavones and maintenance of bone mineral density in post-menopausal women.

Reduction of vasomotor symptoms associated with menopause

The claimed effect which is eligible for further assessment relates to the reduction of vasomotor symptoms associated with menopause. The proposed target population is peri- and post-menopausal women. The Panel considers that reduction of vasomotor symptoms associated with menopause is a beneficial physiological effect.

Five of the 13 RCTs which investigated the effect of soy isoflavones on frequency of hot flushes considered a total of 575 subjects for data analysis (30-119 subjects per group) with daily soy isoflavone doses of 27 to 100 mg for 3-24 months and reported a statistically significant effect of soy isoflavones on frequency of hot flushes, whereas six studies, which considered 623 subjects for data analysis (12-100 subjects per group/period) and provided 40 to 120 mg of soy isoflavones per day for six weeks to six months, did not report an effect of soy isoflavones on frequency of hot flushes, while one study did not report results of this outcome. In one study in 75 subjects, in which 70 mg/day soy isoflavones were administered for 16 weeks, the per protocol and intention-to-treat analyses led to inconsistent results with respect to an effect of soy isoflavones on hot flush frequency. The Panel notes that two of the studies might have been underpowered to detect a statistically significant effect of soy isoflavones on frequency of hot flushes.

Six of the 12 RCTs which investigated the effect of soy isoflavones on severity of hot flushes considered a total of 567 subjects for data analysis (25-119 per group) with daily soy isoflavone doses of 27 to 100 mg for 3-12 months and reported a statistically significant effect of soy isoflavones on severity of hot flushes, whereas six studies, which considered 668 subjects for data analysis (12-100 subjects per group/period) and provided 40 to 120 mg of soy isoflavones per day for six weeks to six months, did not report an effect of soy isoflavones on the severity of hot flushes.

The three RCTs in which the effect of soy isoflavones on frequency and/or severity of night sweats was examined did not find any statistically significant difference between groups.

The Panel notes that most of these RCTs were at high risk of bias due to major methodological weaknesses in the statistical analyses performed (e.g. inadequate handling or no consideration of missing data, repeated measures and/or multiple comparisons not taken into account, analysis of data with a high risk of not being normally distributed by parametric tests without verification of the assumption of the statistical test applied), and/or that data were inadequately reported.

In weighing the evidence, the Panel took into account that the evidence provided by 15 human intervention studies is inconsistent with respect to an effect of soy isoflavones on reduction of vasomotor symptoms. The Panel also took into account that most of these studies were at high risk of bias, that the inconsistent results could not be explained by dose, sample size, study duration, or baseline frequency or severity of vasomotor symptoms, and that the evidence of the proposed mechanism of action is weak.

On the basis of the data presented, the Panel concludes that the evidence provided is insufficient to establish a cause and effect relationship between the consumption of soy isoflavones and reduction of vasomotor symptoms associated with menopause.

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INTRODUCTION

The Commission has agreed with EU Member States that a certain number of Article 13 health claims would be eligible for further assessment by EFSA in order to be able to take a final decision on whether or not to include these claims in the list of permitted health claims. These claims include already assessed claims related to micro-organisms which the Panel considered to be not sufficiently characterised and claims for which the NDA Panel concluded that there was insufficient evidence to establish a cause and effect relationship between the consumption of the food and the claimed effect.

Following two opinions of the NDA Panel pursuant to Article 13 of Regulation (EC) No 1924/2006[5] in which the Panel concluded that the evidence provided was insufficient to establish a cause and effect relationship between soy isoflavones and maintenance of bone mineral density and reduction of vasomotor symptoms associated with menopause (EFSA Panel on Dietetic Products Nutrition and Allergies (NDA), 2009, 2011), EFSA received additional information from the competent Authorities of Germany and Austria for the further assessment of these claims.

ASSESSMENT

1. Characterisation of the food/constituent

The food constituent that is the subject of the health claims is soy isoflavones.

Soy isoflavones constitute a wide range of compounds of plant origin, which mainly comprise genistein, daidzein and glycitein, among others (Ma et al., 2008a, 2008b). Soy isoflavones can be consumed as isolated soybean protein, as whole-soybean foods, or as supplements containing extracts, pure compounds or mixtures (Cassidy et al., 2006).

The Panel considers that the food constituent, soy isoflavones, which is the subject of the health claims, is sufficiently characterised.

2. Relevance of the claimed effect to human health

2.1. Maintenance of bone mineral density (ID 1655)

The claimed effect which is eligible for further assessment relates to the maintenance of bone mineral density. The proposed target population is post-menopausal women.

Bone health relates to bone mass, bone mineral density (BMD) and bone structure, which all contribute to bone strength. Whereas bone structure and bone strength are usually not measured *in vivo*, BMD is a good indicator of bone health in the general population.

After menopause, an increased rate of bone loss and bone remodelling, and a decrease in BMD, are observed. These changes have been associated with an increased risk of bone fractures. BMD, a relevant factor for the assessment of bone health, can be measured by established methods.

The Panel considers that maintenance of bone mineral density is a beneficial physiological effect.

2.2. Reduction of vasomotor symptoms associated with menopause (ID 1654, 1704, 2140, 3093, 3154, 3590)

The claimed effect which is eligible for further assessment relates to the reduction of vasomotor symptoms associated with menopause. The proposed target population is peri- and post-menopausal women.

Changes in vasomotor symptoms associated with menopause such as frequency and severity of hot flushes and night sweats can be assessed using questionnaires.

[5] Regulation (EC) No 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods. OJ L 404, 30.12.2006, p. 9–25.

The Panel considers that reduction of vasomotor symptoms associated with menopause is a beneficial physiological effect.

3. Scientific substantiation of the claimed effect

3.1. Maintenance of bone mineral density (ID 1655)

In a previous evaluation of this claim, two meta-analyses of randomised controlled trials (RCTs) (Ma et al., 2008a, 2008b) and one systematic review of randomised clinical trials (RCTs) (Cassidy et al., 2006) which investigated the effects of soy isoflavones on biochemical markers of bone turnover (Ma et al., 2008b), BMD (Ma et al., 2008a), or both (Cassidy et al., 2006), in post-menopausal women were evaluated for the scientific substantiation of the claim. All the individual studies presented at that time had been considered in these publications. Publications on the health effects of phytoestrogens in general, or on the effects of soy isoflavones on health outcomes unrelated to bone status, were not considered pertinent to the evaluation of the claim.

The additional information provided for further assessment included narrative reviews on the effects of soy isoflavones on different aspects of bone metabolism in animals and humans, both *in vivo* and *in vitro*, which contained no original data which could be used for the scientific substantiation of the claim; one publication on dietary phytoestrogen and isoflavone intakes; and four publications reporting on subgroup analyses, safety data, or cardiovascular/systemic inflammation-related outcomes of primary studies conducted to address the effects of soy isoflavones on bone (Atteritano et al., 2009; Chen et al., 2004; Gertz et al., 2010; Wu et al., 2006a). The Panel considers that no conclusions can be drawn from these references for the scientific substantiation of the claim.

This evaluation is based on the scientific references provided in the present and the previous submission which addressed the effects of soy isoflavones on BMD in peri- and/or post-menopausal women, and/or the mechanisms by which soy isoflavones could exert the claimed effect in the target population.

3.1.1. Human data

3.1.1.1. Human intervention studies on bone mineral density

The Panel notes that changes in bone mass which result from a change in the remodelling balance last for the duration of one remodelling cycle (at least six months) but may not be retained in subsequent remodelling cycles (i.e. the remodelling transient), so that at least 12 months are needed to evaluate the short-term impact of an intervention on BMD, whereas 2–3 years are necessary to evaluate the long-term effects. The Panel also notes that studies lasting <6 months provide no useful information about the effects of an intervention on BMD.

A total of 31 human intervention studies were submitted, either individually or as part of systematic reviews/meta-analyses of RCTs, on the effects of soy isoflavones on BMD. Among these, five were published in Chinese and no translation into an EU language was available (Dong et al., 2008; Gao et al., 2006; Xin and Yang, 2006; Ye et al., 2006; Yi and Shu, 2004), one was of three months duration (Uesugi et al., 2003), one was conducted in pre-menopausal women (Anderson et al., 2002), one primarily (85 % of subjects) in males (Newton et al., 2006), one used an isoflavone metabolite (*S*-equol) as intervention (Tousen et al., 2011), and one was a single-arm, open label, uncontrolled study (Scheiber et al., 2001). The Panel considers that no conclusions can be drawn from these studies for the scientific substantiation of the claim.

Table 1 depicts the characteristics of the remaining 21 human intervention studies, which are discussed below, by duration of the intervention (≥12 months, <12 months). BMD was assessed by dual-energy x-ray absorptiometry (DXA) in all the studies.

Table 1 Study characteristics of human intervention studies which assessed the effect of soy isoflavones on BMD in peri- and post-menopausal women with duration of the intervention ≥12 months (n=14) and 6-12 months (n=7).

Author	PY	Duration (mo)	IF dose (mg/d)	BMD criteria (TS)	(y) since menopause	Randomised (n)	Completers /compliers (n)	Attrition rate (%)	Statistical analysis	Power calculation	Primary outcome	BMD	Bone formation	Bone resorption
≥ 12 months														
Alekel	2010	36	0 80 120	LS/TPF ≥ -1.5 SD and < +1SD	2.7 (1.9, 5.3) 3.0 (1.8, 5.2) 2.8 (1.7, 4.8)	83 87 85	74/72 77/67 73/69	11 11 14	MITT PP	Post-hoc	BMD LS and FN	WB, LS, TPF, FN	B-ALP	CTx
Arjmandi	2005	12	0 60	NR	6±5 5±5	39 48	27 35	31 27	Completers	No	Unclear	WB, LS, FN	B-ALP, osteocalcin	DPYR
Brink	2008	12	0 110	LS ≥ -2SD	<5	150 150	118 119	22 22	Completers	Yes	WB BMD	WB, LS	B-ALP, PINP	PYR, DPYR
Chen	2003	12	4 40 80	NR	4.1 ± 2.4 3.9 ± 2.2 4.4 ± 2.5	67 68 68	58/53 62/57 54/50	13 9 21	Completers PP	No	Unclear	WB, LS, TPF, FN, FT, intertrochanter	---	---
Huang	2006	12	0 100 200	NR	4.4 ± 1.2 5.6 ± 1.3 3.1 ± 0.9	13 15 15	12 15 15	8 0 0	Completers	No	BMD (unspecified)	WB, LS, FN, FT, WT	B-ALP	NTx, DPYR
Kenny	2009	12	0+AP 0+SP 105+AP 105+SP	LS/TPF ≥ -3SD	22.8 ± 8.1 24.3 ± 10.8 22.6 ± 9.3 23.5 ± 9.9	33 34 32 32	22 24 26 25	33 29 19 22	Completers	Post-hoc	Site with the lowest changes in BMD	WB, LS, TPF, FN, FT, WT, radius	B-ALP	NTx
Kreijkamp-Kaspers	2004	12	0 99	NR	18.5 ± 7.5 18.0 ± 6.0	102 100	87/78 88/75	15 12	MITT PP	Yes	BMD LS	LS, TPF, FN, FT, WT, intertrochanter	B-ALP	---
Levis	2011	24	0 200	LS/TPF ≥-2SD	<5	126 122	99/88 83/71	21 32	Completers PP	Yes	BMD LS	LS, TPF, FN,	---	NTx
Lydeking-Olsen	2004	24	0 0+TDP 76+TDP 76	LS or TPF ≥ -2SD	6.0 (1–29) 9.5 (1–26) 10.5 (1–30) 6.0 (1–26)	28 27 26 26	22 22 22 23	22 19 15 12	Completers	Yes	BMD LS and TPF	WB, LS, TPF, FN, FT, WT	PINP	ICTP
Marini	2007	24	0 54	FN, <-1SD	4.9 ± 3.2 5.6 ± 3.8	191 198	154 150	19 25	ITT	Yes	BMD LS and FN	LS, FN	B-ALP, osteocalcin	PYR, DPYR
Morabito	2002	12	0 0+HRT 54	FN, <-1SD	6 ± 5 7±6 7± 3	NR	30 30 30	NR	MITT	No	BMD (unspecified)	LS, FN	B-ALP	PYR, DPYR
Vupad-hyayula	2009	24	0 (SP) 0 (MP) 90	LS/TPF ≥-2SD	14 ± 0.7 14.6 ± 0.6 15.1± 0.8	65 69 69	48/20 57/30 52/35	26 17 15	MITT Completers	Yes	BMD LS and TPF	WB, LS, TPF, FN, FT	---	NTx
Wong	2009	24	0 80 120	LS, ≥-1SD	6.5 ± 5.3 6.4 ± 5.2 6.9 ± 6.5	135 135 136	126 119 117	7 12 14	Completers	Yes	BMD LS	WB, LS, TPF, FN, FT	B-ALP, osteocalcin	NTx

Author	PY	Duration (mo)	IF dose (mg/d)	BMD criteria (TS)	(y) since menopause	Randomised (n)	Completers /compliers (n)	Attrition rate (%)	Statistical analysis	Power calculation	Primary outcome	BMD	Bone formation	Bone resorption
Wu	2006	12	0 0+walk 47 47+walk	NR	3.7 ± 2.1 3.6 ± 1.8 2.7 ± 1.4 3.2 ± 1.4	34 34 34 34	29 24 25 30	15 29 26 12	Completers	No	Unclear	WB, LS, TPF, FN	B-ALP, osteocalcin	DPYR
< 12 months														
Alekel	2000	6	0 + WP 4.4 + SPI 80.4+SPI	NR	19 (1–70) * 17 (1–79) 14 (1–49)	NR	21 24 24	NR	Completers	Yes	BMD LS	LS	B-ALP	NTx
Evans	2007	9	0 + MP 0+MP+EX 91 91+EX	NR	8.9 ± 5.2 4.9 ± 5.6 7.6 ± 4.9 8.4 ± 5.9	61	12 10 10 11	30	ITT Completers	No	BMD and turnover (unspecified)	WB, LS, TPF, FN, FT, intertrochanter	B-ALP	CTx
Gallagher	2004	9	<4 52 96	NR	7.3 ± 1.5 8.9 ± 1.1 6.5 ± 1.3	65	14 19 17	33	Completers	Yes	BMD LS	LS, FN, FT	B-ALP	NTx
Harkness	2004	6	0 110	LS/TPF ≥-2.5SD	19.1 ± 5.5	20	19	5	Completers	No	Unclear	LS, FN, FT, intertrochanter	B-ALP, osteocalcin	HP
Turhan	2008	6	0 40		4.0 ± 1.7 3.3 ± 1.9	45 45	37 43	18 5	Completers	Yes	CTx	LS, FN, WT	B-ALP, osteocalcin	CTx
Potter	1998	6	0 56 90	NR	12.6 ± 8.5 12.2 ± 9.7 13.7 ± 8.3	81	22 23 21	19	Completers	No	Unspecified	WB, LS, FN, WT	---	---
Ye	2006	6	0 84 126	NR	2.9 ± 1.6 2.6 ± 1.4 2.3 ± 1.5	30 30 30	30/27 28/26 26/25	0 7 13	Completers	No	Unspecified	LS, TPF, FN, FT, intertrochanter	B-ALP, osteocalcin	DPYR

AP = animal protein
B-ALP = bone alkaline phosphatase
BMD = bone mineral density
CTx = cross-linked C-telopeptides of type 1 collagen
DPYR = deoxypyridinoline cross-links
EX = exercise
FN = femoral neck
FT = femoral trochanter
HRT = hormone replacement therapy
HP = type 1 collagen α_1-chain helical peptide
ICTP = type-1 C-terminal telopeptide
IF = isoflavones
ITT = intention-to-treat
LS = lumbar spine
MITT= modified intention to treat
MP = milk protein
NR = not reported
NTx = cross-linked N-telopeptides of type 1 collagen
PINP = type-1 procollagen N-terminal peptide
PP = per protocol
PY = publication year
PYR = pyridinoline cross-links
SD = standard deviation
SP = soy protein
TDP = transdermal progesterone
TPF = total proximal femur
TS = T score
WB = whole body
WP = whey protein
WT = Ward's triangle
Completers = analysis carried out in all subjects completing the study
* In weeks since last menses

(a) Interventions lasting ≥12 months

In 14 studies, the intervention with soy isoflavones lasted ≥12 months (see Table 1). All the studies were randomised, had a parallel design, and all but one (open label, Huang et al., 2006) were double blind. All were conducted in post-menopausal women, but were very heterogeneous regarding mean age, years since last menses, and bone status. Isoflavones were consumed in capsules in eight studies, either extracted from soy germ (Chen et al., 2003; Wong et al., 2009), from soy beans/protein (Alekel et al., 2010; Huang et al., 2006; Levis et al., 2011), from an undisclosed source (Wu et al., 2006b), or provided as pure genistein from undisclosed origin (Marini et al., 2007; Morabito et al., 2002). Soy isoflavones were consumed as part of soy foods (e.g. soy protein, soy milk and other soy foods) in the remaining six studies. The isoflavone dose ranged from 40 to 200 mg/day. The genistein, daidzein and glycitein contents were widely variable, ranging between 12-100 %, 25-55 %, and 1-33 % of total isoflavones, respectively. Changes in BMD were assessed at the total body (n=8), lumbar spine (n=14), total hip (n=9), femoral neck (n=12), femoral trochanter (n=8), Ward's triangle (n=6) and inter-trochanter area (n=2). All but three studies assessed markers of bone formation, and all but two assessed markers of bone resorption.

Two studies (Marini et al., 2007; Morabito et al., 2002) from the same research group reported a statistically significant effect of soy isoflavones at doses of 54 mg/day on BMD at all sites measured, together with a significant decrease in markers of bone resorption and a significant increase in markers of bone formation.

In the study by Morabito et al. (2002), post-menopausal women aged 47-57 years with osteopenia or osteroporosis at the femoral neck were randomised to consume 54 mg/day isoflavones, hormone replacement therapy (HRT), or placebo for one year. A total of 30 women per group completed the study. The Panel notes that no information is available on the number of women originally randomised, attrition rates, or reasons for losses to follow up. BMD (as % changes from baseline) significantly increased at the three bone sites measured (lumbar spine, femoral neck and Ward's triangle) in the HRT (by 4 %, 2.5 % and 3 %, respectively) and soy isoflavone (by 3 %, 5.5 % and 4 %, respectively) groups compared to placebo, with no significant differences between the HRT and the soy isoflavone groups. Markers of bone resorption significantly decreased in the HRT and soy isoflavone groups compared to placebo, whereas markers of bone formation significantly increased in the isoflavone group and significantly decreased in the HRT group compared to placebo. The Panel considers that this study shows an effect of soy isoflavones at doses of 54 mg/day on BMD in post-menopausal women.

In a second study (Marini et al., 2007), post-menopausal women aged 49-67 years, with osteopenia or osteroporosis at the femoral neck were randomised to consume daily 54 mg isoflavones or placebo for two years. BMD (in absolute values) significantly increased at the two bone sites measured (lumbar spine and femoral neck) in the soy isoflavone group (from 0.842 to 0.891 g/cm^2 and from 0.667 to 0.702 g/cm^2, respectively) compared to placebo (from 0.837 g/cm^2 to 0.784 g/cm^2 and from 0.674 to 0.638 g/cm^2, respectively; $p<0.001$ for all comparisons). Markers of bone resorption significantly decreased and markers of bone formation (bone alkaline phosphatase (B-ALP)) significantly increased in the soy isoflavone group compared to placebo ($p<0.001$ for pyridinoline cross-links (PYR), and B-ALP; $p=0.002$ for deoxypyridinoline cross-links (DPYR)). The Panel considers that this study shows an effect of soy isoflavones at doses of 54 mg/day on BMD in post-menopausal women.

Four studies each reported a statistically significant change in BMD at only one bone site among a number of sites measured (whole body (Wong et al., 2009); intertrochanter region of the hip (Kreijkamp-Kaspers et al., 2004); femoral neck (Alekel et al., 2010); Ward's triangle (Wu et al., 2006b)) in the soy isoflavone group compared to placebo, with no significant changes in markers of bone formation or resorption. The bone site at which a significant effect of soy isoflavones was reported was never the primary outcome of the study and differed between studies. In addition, no

rationale was provided in these studies for a differential effect of soy isoflavones at the bone sites measured, so that chance findings cannot be excluded.

Wong et al. (2009) randomised post-menopausal women aged 40-60 years with normal BMD at the lumbar spine to consume 0 (placebo), 80 or 120 mg soy isoflavones daily for two years. The primary outcome was changes in BMD at the lumbar spine, which were used for power calculations. A significant increase in whole body BMD was reported for the highest soy isoflavone dose only compared to placebo, whereas no changes in whole body bone mineral content (BMC) were observed between groups. No significant differences were observed between groups for changes in BMD at any bone site (lumbar spine, total hip, femoral neck, femoral trochanter), nor for changes in markers of bone formation or resorption. The Panel notes that no effect of soy isoflavones was observed on the primary outcome (lumbar spine) or on any region of the hip. The Panel considers that this study does not show an effect of soy isoflavones at doses up to 120 mg/day on BMD in post-menopausal women.

Kreijkamp-Kaspers et al. (2004) randomised post-menopausal women (mean age about 66.5 years) with normal BMD at the lumbar spine to consume daily 99 mg isoflavones in soy protein or placebo (milk protein) for one year. Changes in BMD at the lumbar spine were used for power calculations. No significant differences were observed between groups for changes in BMD at any bone site measured (lumbar spine, total hip, femoral neck, femoral trochanter, Ward's triangle), except for the intertrochanter region of the hip, where BMD showed a decrease of 0.009 g/cm^2 in the placebo and an increase of 0.004 g/cm^2 in the isoflavone group, resulting in a difference in BMD change of 1.31 % (p=0.02). No changes were observed with respect to changes in bone formation (B-ALP). Bone resorption was not assessed. Calcium and potassium excretion did not differ between groups. The Panel notes that no effect of soy isoflavones was observed on the primary outcome (lumbar spine) or on any other region of the hip. The Panel considers that this study does not show an effect of soy isoflavones at doses of 99 mg/day on BMD in post-menopausal women.

In the study of longest duration, Alekel et al. (2010) randomised post-menopausal women aged 45.8-65.0 years with normal BMD at the lumbar spine and proximal femur to consume 0, 80 or 120 mg/day soy isoflavones in capsules for three years. Power calculations were only performed *post-hoc*. The overall response (percentage change from baseline to three years) of the lumbar spine, total proximal femur, proximal neck, and whole body BMD to the isoflavone intervention was not significant in the (modified) intention-to-treat (MITT) model. In the per protocol (PP) analysis, the 120 mg dose showed a protective effect (p=0.024) on percent decline for BMD at the femoral neck, but not for other BMD outcomes, compared to placebo. No significant differences were noted between groups regarding markers of bone formation or resorption. The Panel considers that this study does not show an effect of soy isoflavones at doses up to 120 mg/day on BMD in post-menopausal women.

Wu et al. (2006b) randomised post-menopausal women (mean age about 55 years) to consume daily 47 mg soy isoflavones with or without three 45-min walking sessions per week or placebo (± walking) for one year. The Panel notes that the origin and composition of soy isoflavones was not reported, that participants were not selected on the basis of bone status, and that the primary outcome of the study was not identified. A significant effect of walking was reported with respect to changes in BMD at the total hip (p=0.04), whereas a significant effect of both walking (p=0.0001) and the soy isoflavone intervention (p=0.04) was reported for changes in BMD at the Ward's triangle, with no interaction between them. The Panel notes that no significant differences were observed between groups for changes in whole body BMD or BMD at the lumbar spine, femoral neck or femoral trochanter. No significant differences were observed with respect to changes in markers of bone formation or resorption. The Panel considers that this study does not show an effect of soy isoflavones at doses of 47 mg/day on BMD in post-menopausal women.

Two studies (Huang et al., 2006; Lydeking-Olsen et al., 2004) reported inconsistent effects of soy isoflavones on BMD across study arms for which no explanation was provided, so that chance findings cannot be excluded.

Lydeking-Olsen et al. (2004) randomised post-menopausal women without osteoporosis to consume daily 76 mg soy isoflavones in soy milk with or without transdermal progesterone (540 mg micronised progesterone per three week cycle equivalent to 25.7 mg/day) or soy milk without isoflavones (± transdermal progesterone) for two years. Primary outcomes used for power calculations were changes in BMD at the lumbar spine and total hip. A significant effect of soy isoflavones when given alone was reported for changes in BMD (as % from baseline) at the lumbar spine (+1.1 %) compared to placebo (–4.2 %, p=0.009), but not when given in combination with transdermal progesterone (–2.8 %), which had no significant effect on BMD at the lumbar spine (+2.0 %) when compared to placebo. The Panel notes that no evidence has been provided for a negative interaction between progesterone and soy isoflavones on BMD changes at the lumbar spine. No significant differences were observed between groups for changes in BMD at the femoral neck, femoral trochanter or Ward's triangle. The Panel considers that this study does not show an effect of soy isoflavones at doses of 76 mg/day on BMD in post-menopausal women.

In the only open label study provided (Huang et al., 2006), which also had the smallest sample size per study group, post-menopausal women aged 45–67 years were randomised to consume 0, 100 or 200 mg soy isoflavones per day in capsules for one year. The Panel notes that subjects were not recruited on the basis of their bone status and that the primary outcome was not specified. Results for changes in BMD at the lumbar spine were given for each vertebra (L1 to L4) separately, and for six combinations of them. BMD (as % change from baseline) significantly increased in the 100 mg/day soy isoflavone group at L1-3, L1-4 and L2-4 compared to placebo and at L1-3 compared to the 200 mg/day soy isoflavone group. No significant differences in BMD changes at the lumbar spine were noted between the 200 mg/day isoflavone group and controls. Conversely, a significant increase in BMD at the femoral neck was observed in the 200 mg/day isoflavone group compared to the control group (0.24 % vs. -2.32 %, $p<0.05$) whereas the 100 mg/day isoflavone dose had no effect (-0.66 %). No dose-response was noted for these changes in BMD at the femoral neck across study groups. No significant differences in BMD changes at the femoral trochanter or Ward's triangle were reported between groups. The Panel notes that the observed differences between the study groups at different bone sites cannot be explained by the dose of soy isoflavones administered and no alternative explanation has been provided. The Panel considers that this study does not show an effect of soy isoflavones at doses up to 200 mg/day on BMD in post-menopausal women.

The remaining six studies (Arjmandi et al., 2005; Brink et al., 2008; Chen et al., 2003; Kenny et al., 2009; Levis et al., 2011; Vupadhyayula et al., 2009) did not show an effect of soy isoflavones on BMD at any of the bone sites measured (i.e. whole-body, n=5; lumbar spine, n=6; total hip, n=5; femoral neck, n=4; femoral throchanter, n=3; intertrochanter region, n=1; Ward's triangle, n=1), or on markers of bone formation (n=5) or resorption (n=4).

Among the 14 studies provided which addressed the effects of soy isoflavones on BMD at different bone sites in post-menopausal women, only two by the same research group (Marini et al., 2007; Morabito et al., 2002) reported an effect of soy isoflavones at doses of 54 mg/day at the lumbar spine and femoral neck which was accompanied by a significant increase in markers of bone formation and a significant decrease in markers of bone resorption. Both studies were performed in early post-menopausal women with osteopenia or osteoporosis. The remaining 12 studies used doses of isoflavones up to 200 mg/day and showed no effect of soy isoflavones on BMD. None of these 12 studies reported an effect of soy isoflavones on markers of bone formation or resorption. The Panel notes that five of these studies may have been underpowered to detect an effect of the intervention on bone (Arjmandi et al., 2005; Huang et al., 2006; Kenny et al., 2009; Lydeking-Olsen et al., 2004; Wu et al., 2006b).

The Panel notes that of 14 studies lasting ≥12 months, two studies, one of which had 30 subjects per intervention arm, showed an effect of soy isoflavones on BMD at doses of 54 mg/day, whereas 12, seven of which had a sample size per study arm of at least 50 subjects, did not show an effect at doses of 40 to 200 mg/day. The Panel also notes that these inconsistent findings may not be explained by differences in study size, dose of soy isoflavones used, duration of the intervention, or post-menopausal status.

(b) Interventions lasting <12 months

In seven studies the intervention lasted between six and nine months (see Table 1).

The study by Harkness et al. (2004) had a cross-over design with no wash-out period. The Panel notes that the presentation (by treatment and intervention period, four periods) and analysis (multiple paired *t*-test for within [before and after] and between period, and between group [end values only], comparisons) of the results are inadequate for cross-over designs. Similarly, the study by Turhan et al. (2008), with a parallel design, did not provide any direct comparison between the intervention and control groups for changes in the outcome variables of interest. The Panel considers that no conclusions can be drawn from these studies for the scientific substantiation of the claim.

All the remaining studies (n=5) were randomised and had a parallel design, and all but one (single blind, Ye et al., 2006) were double blind. All were conducted in post-menopausal women, but were very heterogeneous regarding mean age, years since last menses, and bone status. Isoflavones were consumed in capsules (extracted from soy germ) in one study (Ye et al., 2006), and as part of soy foods (e.g. soy protein, soy milk and other soy foods) in the remaining four studies. The soy isoflavone dose ranged from 52 to 126 mg/day. In the two studies which reported this information, the genistein, daidzein and glycitein contents were very variable, ranging between 15-54 %, 30-52 % and 0.5-33 %, respectively. Changes in BMD were assessed at the lumbar spine (n=5); total hip (n=2); femoral neck (n=4); femoral trochanter (n=3), Ward's triangle (n=1), inter-trochanter area (n=2); and total body (n=2). All studies but one (Potter et al., 1998) assessed markers of bone formation and bone resorption.

In the study by Gallagher et al. (2004), in which power calculations were performed considering percent changes from baseline in BMD at the lumbar spine, post-menopausal women were randomised to consume soy protein isolate providing <4 (control), 52 or 96 mg/day isoflavones for nine months. No significant changes in BMD (% change from baseline) at the lumbar spine or femoral neck were observed between groups, whereas BMD at the femoral trochanter increased significantly in the control group compared to the groups consuming 56 mg/day (p=0.02) and 96 mg/day (p=0.002) isoflavones. No significant differences in markers of bone turnover were observed between groups during the intervention. The Panel considers that this study does not show a beneficial effect of soy isoflavones on BMD in post-menopausal women.

Evans et al. (2007) randomised post-menopausal women (62±5 years) to consume milk protein isolate (no isoflavones) or soy protein isolate (91 mg/day isoflavones), with or without exercise, for nine months. Neither soy isoflavones nor exercise showed an effect on changes in whole body BMD or BMD at the lumbar spine, total hip, femoral neck, femoral trochanter or inter-trochanter area. Soy isoflavones significantly decreased markers of bone formation and resorption (in the completers analysis only), whereas exercise had no effect. The Panel notes that transient changes in markers of bone turnover did not lead to changes in BMD in this study. The Panel considers that this study does not show an effect of soy isoflavones at doses of 91 mg/day on BMD in post-menopausal women.

Ye et al. (2006) randomised post-menopausal women to consume 0, 84 or 126 mg/day isoflavones from soy germ for six months. The Panel notes that the primary outcome was not specified. No significant differences were observed between groups for changes in BMD at the total hip, femoral trochanter or intertrochanter area. A significant positive linear trend was reported for an effect of soy isoflavones on BMD at the lumbar spine (% changes) and femoral neck (in absolute values and % changes). Differences between intervention and placebo groups were statistically significant for

the highest isoflavone dose (126 mg/day) compared to placebo. Although a transient decrease in DPYR, a marker of bone resorption, was observed in the 126 mg/day isoflavone group compared to the lowest dose group and placebo at three months, no significant differences were noted between groups for markers of bone formation or resorption at six months. The Panel considers that this study shows an effect of soy isoflavones on BMD at the lumbar spine and femoral neck at doses of 126 mg/day. This study suggests that the change in BMD may be associated with transient changes in bone resorption, and that the effect might be dose-dependent.

In the study by Alekel et al. (2000), in which power calculations were performed considering percent changes from baseline in BMD at the lumbar spine, peri-/post-menopausal women (median age: 50.6 years) were randomised to consume whey protein without isoflavones (control), or soy protein isolate providing 4 or 80 mg/day isoflavones for six months. No treatment effect was observed on BMD at the lumbar spine by analysis of covariance having baseline BMD as covariate. When various factors which could have contributed to changes in BMD were taken into account by using multiple regression analyses, the 80 mg/day isoflavone intervention had a significant positive treatment effect on the percentage change (loss) in BMD at the lumbar spine (5.6 %; p=0.023), whereas the other two interventions did not. No significant differences between groups were observed with respect to markers of bone formation or resorption. The Panel considers that this study shows an effect of soy isoflavones on BMD at the lumbar spine in post-menopausal women.

In the study by Potter et al. (1998), post-menopausal women were randomised to consume isolated soy protein providing 56 or 90 mg/day isoflavones or casein and non-fat dry milk without isoflavones (control) for six months. The Panel notes that the primary outcome was not specified. A significant increase in BMD at the lumbar spine was observed only in the group receiving 90 mg/day soy isoflavones compared to controls. No effect of the intervention was detected on BMD at the femoral neck or Ward's triangle in any of the soy isoflavone groups. Markers of bone turnover were not assessed. The Panel considers that this study suggests an effect of soy isoflavones on BMD at the lumbar spine in post-menopausal women.

Among the five human intervention studies which allowed conclusions to be drawn on the effects of soy isoflavones administered for six to nine months on BMD in peri-/post-menopausal women, one (Ye et al., 2006) showed a beneficial dose-response effect on BMD at the lumbar spine and femoral neck at doses of 84 and 126 mg/day which may have been associated with a transient decrease in bone resorption, two reported a beneficial effect of 80 mg/day (Alekel et al., 2000) and 90 mg/day (Potter et al., 1998) soy isoflavones on BMD at the lumbar spine with no effect on markers of bone turnover, and two studies using doses of soy isoflavones of 91 mg/day (Evans et al., 2007) and 52 and 96 mg/day (Gallagher et al., 2004), one of which reported a significant decrease in markers of bone formation and resorption in the soy isoflavone group, showed no effect of soy isoflavones on BMD at any site.

The Panel notes the exploratory nature and small sample size of these studies. However, the Panel considers that they provide some evidence for an effect of soy isoflavones on the attenuation of BMD loss at the lumbar spine in post-menopausal women when consumed for six to nine months, possibly mediated by a decrease in bone resorption. The Panel also notes that such changes in BMD at the lumbar spine may result from a change in the remodelling balance which may not be retained in subsequent remodelling cycles (i.e. the remodelling transient).

3.1.1.2. Systematic reviews and meta-analyses of RCTs

(a) Bone mineral density

One systematic review (Cassidy et al., 2006) and four meta-analyses of RCTs (Liu et al., 2009; Ma et al., 2008a; Ricci et al., 2010; Taku et al., 2010a) comprising 6, 10, 11, 12 and 12 human intervention studies, respectively, aimed to address the effects of (soy) isoflavones on BMD in post-menopausal women (see Table 2).

Table 2 Studies included in the systematic review and meta-analyses of randomised controlled trials which addressed the effects of soy isoflavones on bone mineral density and markers of bone turnover.

	Bone mineral density					Markers of bone turnover	
	Cassidy et al., 2006	**Ma et al, 2008b**	**Taku et al, 2010b**	**Liu et al, 2009**	**Ricci et al, 2010**	**Ma et al, 2008a**	**Taku et al, 2010a**
Albertazzi et al., 2005							x
Alekel et al., 2000		x			x		
Alekel et al., 2010					x		
Anderson et al., 2002		x		x			
Arjmandi et al., 2003						x	
Arjmandi et al., 2005		x		x	x	x	
Brink et al., 2008			x	x	x		x
Brooks et al., 2004						x	x
Chen et al., 2003	x		x	x			
Clifton-Bligh et al., 2001	x						
Dalais et al., 2003						x	x
Dong et al., 2008			x				
Evans et al., 2007					x		
Gallagher et al., 2004				x	x		
Gao et al., 2006		x	x				
Harkness et al., 2004		x	x				x
Huang et al., 2006			x	x			
Kenny et al., 2009					x		x
Knight et al., 2001							x
Kreijkamp-K. et al., 2004	x	x		x	x		x
Lydeking-Olsen et al., 2004		x		x	x		
Marini et al., 2007			x		x		x
Morabito et al., 2002	x		x			x	x
Mori et al., 2004						x	x
Newton et al., 2006				x			
Nikander et al., 2004						x	x
Potter et al., 1998	x	x			x		
Uesugi et al., 2002						x	x
Uesugi et al., 2003		x	x				
Vupadhyayula et al., 2009					x		
Wu et al., 2006b			x	x			x
Xin and Yang, 2006			x				
Xu et al., 2007							x
Yamori et al., 2002						x	x
Ye et al., 2006			x				x
Yi and Shu, 2004		x					

In *italics* = available in Chinese only; underlined = pre-menopausal women; in **bold** = primarily (85%) in men.

The systematic review by Cassidy et al. (2006) and the meta-analysis by Ma et al. (2008a) only included a limited number of the studies available at present which are pertinent to the claim. In these review publications, already evaluated by EFSA in a previous opinion (EFSA Panel on Dietetic Products Nutrition and Allergies (NDA), 2009), statistically significant effects on spine BMD were described in some short-term RCTs in relation to the dietary intake of soy isoflavones, whereas longer-term interventions (≥12 months) did not support a sustained effect.

The meta-analysis by Liu et al. (2009) aimed to assess the overall long-term effects of soy isoflavone mixtures (in soy foods or extracted from soy beans or soy germ) on BMD at the lumbar spine, total hip and femoral neck expressed as changes from baseline relative to the control group in women. Full-length articles (n=11) reporting on RCTs of at least one year duration with changes in BMD as the primary outcome published in English from January 1990 to March 2008 were included (see Table 2). Studies on pure genistein (Marini et al., 2007; Morabito et al., 2002) were excluded. This meta-analysis did not include five of the RCTs lasting ≥12 months which are considered pertinent to the claim due to a later publication date (Alekel et al., 2010; Kenny et al., 2009; Levis et al., 2011; Vupadhyayula et al., 2009; Wong et al., 2009). The meta-analysis by Taku et al. (2010a) aimed to investigate the effects of soy isoflavone extracts on lumbar spine and hip BMD both in terms of change (mg/cm^2) and percentage change (%) from baseline relative to the control group in post-menopausal women. A total of 11 RCTs (6 to 24 months duration) were selected for analysis. Of these, four were available in Chinese only and could not be evaluated by the Panel (see Table 2). Studies on soy protein or other soy foods containing isoflavones (Alekel et al., 2000; Arjmandi et al., 2005; Brink et al., 2008; Evans et al., 2007; Gallagher et al., 2004; Kenny et al., 2009; Kreijkamp-Kaspers et al., 2004; Lydeking-Olsen et al., 2004; Potter et al., 1998; Vupadhyayula et al., 2009) were excluded. The meta-analysis by Ricci et al. (2010) was designed to investigate the effects of soy isoflavones (both as mixtures in food or extracts) on BMD at the lumbar spine in terms of change (g/cm^2) from baseline relative to the control group in Western peri-/post-menopausal women. Full-length articles (n=12) reporting on RCTs of 6 to 36 months duration published in English from January 1990 to February 2010 were considered for the meta-analysis (see Table 2). Studies in Asian populations (Chen et al., 2003; Huang et al., 2006; Wong et al., 2009; Ye et al., 2006) and studies reporting on % changes in BMD only (Morabito et al., 2002) were excluded.

The Panel notes that RCTs using soy isoflavones as intervention considered in the above-mentioned publications have already been addressed in this opinion individually. The Panel also notes that none of the meta-analyses provided were performed taking into account all available evidence on the effects of soy isoflavones on BMD in post-menopausal women, but rather addressed specific formulations of soy isoflavones (e.g. isoflavone extracts (Taku et al., 2010a); isoflavone mixtures (Liu et al., 2009)) or specific population subgroups (e.g. Western women (Ricci et al., 2010)). The Panel considers that these meta-analyses do not provide additional information on the effects of soy isoflavones on BMD in post-menopausal women.

(b) Markers of bone turnover

Two meta-analyses of RCTs addressed the effects of soy isoflavones on markers of bone turnover (Ma et al., 2008b; Taku et al., 2010b).

The meta-analysis by Ma et al. (2008b) included only a limited number of the studies available at present which are pertinent to the claim. In these review publications, already evaluated by EFSA in a previous opinion (EFSA Panel on Dietetic Products Nutrition and Allergies (NDA), 2009), a statistically significant increase in B-ALP and a statistically significant decrease in DPYR compared to placebo were described in some short-term RCTs (<12 weeks) in relation to the dietary intake of soy isoflavones (37 to 118 mg/day), whereas longer-term interventions (≥12 weeks) did not support a sustained effect. The Panel notes that meaningful changes in markers of bone resorption and bone formation in response to an intervention can only be expected after 12 and 24 weeks, respectively (Prentice et al., 2003).

In the meta-analysis by Taku et al. (2010b), 17 studies published up to July 2009 which assessed the effects of soy isoflavones on markers of bone turnover in peri-/post-menopausal women (10 weeks to 12 months duration) met the inclusion criteria. Osteocalcin, B-ALP, and DPYR were assessed in eight (mean isoflavone intake: 73 mg/day, range: 38-110 mg/day), ten (mean isoflavone intake: 84 mg/day, range: 42-114 mg/day), and ten (mean isoflavone intake: 56 mg/day, range: 14-114 mg/day) studies, respectively. Other markers of bone turnover (cross-linked C-telopeptides of type 1 collagen (CTx), cross-linked N-telopeptides of type 1 collagen (NTx)) were not considered for meta-analysis due to the low number of studies available. A significant decrease in urinary DPYR concentrations and no effect on markers of bone turnover were reported for soy isoflavones compared to placebo. The Panel notes that also this meta-analysis, like Ma et al. (2008b), includes only a subset of the studies which are pertinent to the claim.

The Panel notes the exploratory nature of these meta-analyses, and that markers of bone turnover alone cannot be considered as primary indicators of bone health. However, the Panel considers that these meta-analyses provide some evidence for a transient attenuation of bone resorption which is not accompanied by a significant increase in bone formation associated with the consumption of soy isoflavones.

3.1.2. Non-human data

A number of *in vitro* studies have investigated the extent to which soy isoflavones (namely daidzin, genistin and their aglycone derivatives) may be structurally and functionally related to 17β-oestradiol, particularly in their capacity to bind to the oestrogen receptor β (ERβ) which is most abundant in bone tissue. The effects of genistein and daidzein in osteoblast and osteoclast cell lines have also been studied *in vitro*. All these studies have collectively led to the hypothesis that soy isoflavones may exert an effect on both osteoblasts and osteoclasts through genomic (via the classical ERβ) and nongenomic (mediated by membrane-bound ERβ or other cellular proteins) pathways (Castelo-Branco and Cancelo Hidalgo, 2011). However, whether and to which extent any of these contributes to a reduced loss of BMD in post-menopausal women has not been established.

Similarly, a large number of animal studies, primarily in ovariectomised models of oestrogen deprivation, have been performed using various sources of soy isoflavones (pure compounds vs. mixtures, extracts vs. whole soy foods) in comparison to various control foods, conjugated oestrogen or oestradiol. The primary endpoints in these studies have generally been bone mass of trabecular and/or cortical bone, BMD and, less often, mechanical strength. Secondary measures often included surrogate markers of bone turnover. Results from these studies are inconsistent with respect to the effects that soy isoflavones may exert on markers of bone turnover and bone mass at different sites and in different species (Bawa, 2010; Castelo-Branco and Cancelo Hidalgo, 2011).

3.1.3. Mechanisms of action

It has been proposed that soy isoflavones could have a weak oestrogenic effect on ERβ, and that their effects on bone may resemble those of oestrogen replacement therapy or selective oestrogen receptor modulators (SERM). Thus, the main mechanism which has been proposed for an effect of soy isoflavones on bone mass and metabolism, and which has driven most of the research conducted *in vitro*, in animal models, and in humans to date, is an inhibition of osteoclastic activity leading to a significant reduction in bone resorption in conditions of oestrogen deficiency, together with a mild, and quantitatively less relevant, reduction in bone formation.

Whereas there is some evidence for a transient decrease in bone resorption with no increase in markers of bone formation from short-term human intervention studies, the majority of the longer-term studies (≥12 months) do not show an effect of soy isoflavones on biochemical markers of bone turnover. In addition, the two long-term studies showing a decrease in markers of bone resorption also report a significant increase in markers of bone formation which is not observed with 17β-oestradiol or SERM, but rather the opposite. Thus, from the evidence provided, the Panel

considers that the evidence for a mechanism by which soy isoflavones may exert an effect on bone mass and turnover in post-menopausal women is weak.

In weighing the evidence the Panel took into account that of 14 studies lasting ≥12 months, two studies, one of which had 30 subjects per intervention arm, showed an effect of soy isoflavones on BMD at doses of 54 mg/day, whereas 12, seven of which had a sample size per study arm of at least 50 subjects, did not show an effect at doses of 40 to 200 mg/day. The Panel also took into account that these inconsistent findings cannot be explained by differences in study size, dose of soy isoflavones used, duration of the intervention, or post-menopausal status, that the changes in BMD at the lumbar spine observed in some short-term studies (six to nine months) may result from a change in the remodelling balance which may not be retained in subsequent remodelling cycles (i.e. the remodelling transient), and that the evidence for a mechanism by which soy isoflavones may exert an effect on bone mass and turnover in post-menopausal women is weak.

The Panel concludes that the evidence provided is insufficient to establish a cause and effect relationship between the consumption of soy isoflavones and maintenance of bone mineral density in post-menopausal women.

3.2. Reduction of vasomotor symptoms associated with menopause (ID 1654, 1704, 2140, 3093, 3154, 3590)

In a previous assessment of this claim (EFSA Panel on Dietetic Products Nutrition and Allergies (NDA), 2011), 12 RCTs (Albertazzi et al., 2005; Cheng et al., 2007; Crisafulli et al., 2004; D'Anna et al., 2007; Faure et al., 2002; Han et al., 2002; Khaodhiar et al., 2008; Knight et al., 2001; Kotsopoulos et al., 2000; Nahas et al., 2007; St Germain et al., 2001; Upmalis et al., 2000) were evaluated for the scientific substantiation of the claim. RCTs evaluating outcomes other than vasomotor symptoms, assessing the effect of foods other than soy isoflavones, or RCTs for which confounding could not be excluded or which showed considerable limitations in methodology or reporting, or meta-analyses which included these studies, were not considered pertinent to the evaluation of the claim.

In the framework of further assessment, 23 references, two of which (Basaria et al., 2009; Lethaby et al., 2007) had already been considered in the Panel's previous opinion, were provided as well as a range of comments on the Panel's earlier assessment. The Panel notes that reasons for reaching the conclusions in its earlier assessment have been described in its previous opinion (EFSA Panel on Dietetic Products Nutrition and Allergies (NDA), 2011).

This evaluation combines the scientific references provided in the previous submission and the additional references subsequently submitted for further assessment for this claim on soy isoflavones and reduction of vasomotor symptoms associated with menopause.

Among the 21 additional references provided in the framework of further assessment which have not yet been considered by the Panel was a report on an outcome of a symposium of the North American Menopause Society (The North American Menopause Society, 2011) and two narrative reviews (Kurzer, 2008; Messina and Hughes, 2003) which did not provide any original data for the scientific substantiation of the claim. Two meta-analyses were provided as conference proceedings in abstract form only (Kurzer et al., 2009; Taku et al., 2010c), one human intervention study was not randomised (Battaglia et al., 2009), one study was a single arm uncontrolled study (Chedraui et al., 2011) and one was an open label study (Cancelo Hidalgo and Castelo Branco, 2011). In one RCT, no results were presented in relation to frequency or severity of vasomotor symptoms, but only for the somatic subscale of the Menopause Rating Scale, which not only comprises hot flushes, but also heart discomfort, sleeping problems and muscle and joint problems (Carmignani et al., 2010). One study reported on the number of subjects experiencing an increased or decreased severity, or an increased frequency, of hot flushes in the intervention and control group without presenting a statistical analysis (Pop et al., 2008). In another study (Hachul et al., 2011), differences in the baseline frequency of hot flushes between groups were not taken into account in the analysis, and in

another RCT (Levis et al., 2011) results with respect to the effect of isoflavones on frequency of hot flushes were insufficiently reported. The Panel considers that no conclusions can be drawn from these references for the scientific substantiation of the claim.

The meta-analysis by Bolaños et al. (2010) included 19 RCTs with a duration of at least 12 weeks in peri-/post-menopausal women with hot flushes attributed to climacterium and without a cancer background, in which soy was provided in supplement form, as soy extract or as pure genistein or daidzein, and investigated the effect on vasomotor symptoms. The Panel notes that this meta-analysis contains studies which did not allow conclusions to be drawn on the scientific substantiation of the claim owing to the following limitations: uncertainty as to whether women were on tamoxifen (Albertazzi et al., 1998), uncertainty as to whether subjects were blinded to the intervention (Colacurci et al., 2004), uncertainty on the amount of isoflavones provided (Murkies et al., 1995), or use of medication throughout the study, such as *Cimicifuga racemosa* (L.) Nutt., or therapy for thyroid disease, which could have had an impact on the claimed effect, or subjects started taking antibiotics during the study which was one of the exclusion criteria for the study (Lewis et al., 2006). The Panel considers that no conclusions can be drawn from this meta-analysis for the scientific substantiation of the claim.

The meta-analysis by Bolaños-Diaz et al. (2011) was designed as an indirect comparison of two meta-analyses to evaluate the effects of soy extracts vs. HRT on the reduction of hot flushes. The meta-analysis comparing soy isoflavones to placebo considered studies included in the meta-analysis by Bolaños et al. (2010) plus an additional two RCTs. However, RCTs which used soy in the form of a supplement were excluded from the meta-analysis. The Panel notes that this meta-analysis does not contain the totality of studies which could be considered pertinent to the claim, and considers that no conclusions can be drawn from it for the scientific substantiation of the claim.

Therefore, in this combined evaluation the Panel will consider 15 RCTs, of which 12 were already considered in the previous opinion, on the effect of soy isoflavones on vasomotor symptoms, and three *in vitro* studies related to a possible mechanism by which isoflavones could exert the claimed effect. The characteristics of these 15 RCTs are summarised in Table 3.

Table 3 Study characteristics of human intervention studies which assessed the effect of soy isoflavones on vasomotor symptoms

Author	PY	Duration	Outcome measure	Assessed by	IF dose (mg/d)	Randomised (n)	Completers (n)	Attrition rate (%)	Baseline	Analysis	Power calculation
Albertazzi	2005	6 we	HF frequency HF severity	diaries GCS	90 0	100 (cross-over)	100 99	1	frequency x severity: 7	ITT by LOCF	no
Cheng	2007	12 we	HF frequency HF severity NS frequency NS severity	diaries self-rating scale diaries self-rating scale	60 0	60	26 25	15	severity: 1.4 on a 5-point scale	completers	no
Crisafulli	2004	12 mo	HF frequency	diaries	54 HRT 0	30 30 30	83	12	4.6 HF/day	ITT	no
D'Anna	2009	24 mo	HF frequency HF severity	diaries self-rating scale	27 0	135 130	119 117	11	4.3 HF/day severity: 2.3 on a 3-point scale	completers	yes (*post-hoc*)
Evans	2011	21 we	HF frequency HF severity	diaries diaries/GCS	30 0	42 42	32 36	19	9.5 HF/day severity: 1.9 on a 3-point scale	completers MITT	yes (42 per arm)
Faure	2002	16 we	HF frequency	diaries	70 0	39 36	33 22	27	10 HF/day	PP ITT by LOCF	yes (30 per arm)
Ferrari	2009	12 we	HF frequency	diaries	80 0	85 95	55 66	32	7.8 HF/day	completers	yes (86 per arm)
Han	2002	16 we	HF severity	KI	100 0	41 41	40 40	2	severity: 2.5 on a 3-point scale	ITT by LOCF	no
Khaodhiar	2008	13 we	HF frequency HF severity	diaries self-rating scale	60 40 0	191	49 48 45	26	8 HF/day severity: 2.1 on a 4-point scale	PP	yes (50 per arm)
Knight	2001	12 we	HF frequency HF severity	diaries GCS	77 0	12 12	9 11	17	7.5 HF/day	ITT	no

Kostopoulos	2000	12 we	HF severity	validated questionnaire	118 0	44 50	34 41	20	severity: 0.8 on a 3-point scale	PP	no
Lopes de Sousa	2006	16 we	HF frequency HF severity	diaries diaries	120 0	42 42	77 (groups not reported)	8	6.8 HF/day severity: not reported	completers	no
Nahas	2007	10 mo	HF frequency HF severity	diaries self-rating scale	100 0	40 40	38 38	10	10 HF/day severity: 9 on a 12-point scale	completers	no
St Germain	2001	24 we	HF frequency HF severity NS frequency NS severity	interviewer administered menopausal index	80 4 0	24 24 21	24 24 20	1	10 VMS/week	PP	no
Upmalis	2000	12 we	HF frequency HF severity NS frequency	diaries self-rating scale diaries	50 0	90 87	59 63	31	9 HF/day severity: 2 on a 3-point scale	PP	no

IF = isoflavones
HF = hot flushes
GCS = Greene Climacteric Scale (vasomotor subscale)
ITT = Intention-to-treat
KI = Kupperman Index (vasomotor subscale)
LOCF = last observation carried forward
MITT = modified intention-to-treat
NR = not reported
NS = night sweats
PP = per protocol
PY = publication year
VMS = vasomotor symptoms
Completers = analysis carried out in all subjects completing the study

The Panel notes that most of these RCTs were at high risk of bias due to major methodological weaknesses in the statistical analyses performed (e.g. inadequate handling or no consideration of missing data, repeated measures and/or multiple comparisons not taken into account, analysis of data with a high risk of not being normally distributed by parametric tests without verification of the assumption of the statistical test applied), and/or that data were inadequately reported.

The majority of the studies were conducted as parallel studies, except one (Albertazzi et al., 2005) which was of cross-over design. Isoflavones were consumed as pure genistein (Albertazzi et al., 2005; Crisafulli et al., 2004; D'Anna et al., 2009; Evans et al., 2011), as daidzein-rich isoflavone aglycones from soy germ (Khaodhiar et al., 2008), in soy extracts (Faure et al., 2002; Ferrari, 2009; Lopes de Sousa et al., 2006; Nahas et al., 2007; Upmalis et al., 2000), in soy powder (Knight et al., 2001; Kotsopoulos et al., 2000), in (isolated) soy protein (Han et al., 2002; St Germain et al., 2001), and in a soy bean drink (Cheng et al., 2007).

The Panel notes that group analyses, which were not pre-planned, were performed in two studies (Albertazzi et al., 2005; Khaodhiar et al., 2008), and considers that no conclusions can be drawn from these secondary analyses for the scientific substantiation of the claim. Therefore, only primary analyses of these studies are taken into account for this assessment.

In the majority of the studies, data analyses were carried out in the PP or completers population only, except in six RCTs in which data were analysed in the intention-to-treat (ITT) or MITT population (Albertazzi et al., 2005; Crisafulli et al., 2004; Evans et al., 2011; Faure et al., 2002; Han et al., 2002; Knight et al., 2001). In three of these studies, the last observation was carried forward (LOCF) to impute missing data (Albertazzi et al., 2005; Faure et al., 2002; Han et al., 2002), while in the remaining three studies the method for imputing missing data was not specified.

Ten RCTs investigated the effect of soy isoflavones on both frequency and severity of hot flushes (Albertazzi et al., 2005; Cheng et al., 2007; D'Anna et al., 2009; Evans et al., 2011; Khaodhiar et al., 2008; Knight et al., 2001; Lopes de Sousa et al., 2006; Nahas et al., 2007; St Germain et al., 2001; Upmalis et al., 2000), three investigated frequency only (Crisafulli et al., 2004; Faure et al., 2002; Ferrari, 2009) and two severity only (Han et al., 2002; Kotsopoulos et al., 2000). Three of these studies also investigated the effect of soy isoflavones on night sweats (Cheng et al., 2007; St Germain et al., 2001; Upmalis et al., 2000). In all of these studies, subjects in the intervention and control groups were not different at baseline with regard to the frequency and/or severity of hot flushes and/or night sweats.

In 12 out of 13 studies which investigated the effect of soy isoflavones on the frequency of hot flushes, frequency of hot flushes was self-assessed in symptom diaries, in which the daily symptoms were noted, while in the remaining study by St Germain et al. (2001) this outcome was assessed by an interviewer-administered menopausal index. In the 12 studies which investigated the effect of soy isoflavones on severity of hot flushes, severity of hot flushes was assessed by self-rating scales in five studies (Cheng et al., 2007; D'Anna et al., 2009; Khaodhiar et al., 2008; Nahas et al., 2007; Upmalis et al., 2000), by the vasomotor sub-scale of the Greene Climacteric Scale in three studies (Albertazzi et al., 2005; Evans et al., 2011; Knight et al., 2001), by the vasomotor symptom score of the Kupperman Index in one study (Han et al., 2002), by an interviewer-administered menopausal index in one study (St Germain et al., 2001), by a validated questionnaire in a further study (Kotsopoulos et al., 2000) and by diaries in two other studies (Evans et al., 2011; Lopes de Sousa et al., 2006). In the three of the aforementioned studies investigating night sweats, one study (Upmalis et al., 2000) assessed the frequency of night sweats only, while St Germain et al. (2001) and Cheng et al. (2007) assessed both frequency and severity of night sweats.

Five (Crisafulli et al., 2004; D'Anna et al., 2009; Evans et al., 2011; Ferrari, 2009; Nahas et al., 2007) of the 13 RCTs which investigated the effect of soy isoflavones on frequency of hot flushes reported a statistically significant effect of soy isoflavones on this outcome. These five studies together considered 575 subjects for data analysis (30-119 subjects per group) and provided 27 to 100 mg soy isoflavones per day for 3-24 months. Power calculations were performed in three of

these studies (D'Anna et al., 2009; Evans et al., 2011; Ferrari, 2009), which were reported to be powered to detect a difference of two hot flushes per day between groups (Ferrari, 2009), or a 20 to 35 % difference in change from baseline between groups (D'Anna et al., 2009; Evans et al., 2011). Conversely, six studies (Albertazzi et al., 2005; Khaodhiar et al., 2008; Knight et al., 2001; Lopes de Sousa et al., 2006; St Germain et al., 2001; Upmalis et al., 2000) which considered 623 subjects for data analysis (12-100 subjects per group/period) and provided 40 to 120 mg of soy isoflavones per day for six weeks to six months did not report an effect of soy isoflavones on the frequency of hot flushes, while one study (Cheng et al., 2007) did not report results of this outcome. Power calculations were performed in one of these studies (Khaodhiar et al., 2008), which was reported to have been powered to detect a difference in change from baseline of 1.2 hot flushes per day between groups. In one study (Faure et al., 2002) in 75 subjects, in which 70 mg/day soy isoflavones were administered for 16 weeks and which was powered to detect a difference of three hot flushes per day between groups, the PP and ITT analyses led to inconsistent results with respect to an effect of soy isoflavones on hot flush frequency. The Panel notes that the studies by Knight et al. (2001) and St. Germain et al. (2001) might have been underpowered to detect a statistically significant effect of soy isoflavones on frequency of hot flushes.

Five (Cheng et al., 2007; D'Anna et al., 2009; Han et al., 2002; Nahas et al., 2007; Upmalis et al., 2000) of the 12 RCTs which investigated the effect of soy isoflavones on severity of hot flushes reported a statistically significant effect of soy isoflavones on this outcome. In these studies a total of 567 subjects were considered for data analysis (25-119 per group) and provided 27 to 100 mg soy isoflavones per day for 3-24 months. Conversely, seven studies (Albertazzi et al., 2005; Evans et al., 2011; Khaodhiar et al., 2008; Knight et al., 2001; Kotsopoulos et al., 2000; Lopes de Sousa et al., 2006; St Germain et al., 2001) did not report an effect of soy isoflavones on the severity of hot flushes. In these studies, 668 subjects entered data analysis (12-100 subjects per group/period) and provided 40 to 120 mg of soy isoflavones per day for six weeks to six months. Only one study (Khaodhiar et al., 2008) presented power calculations for this outcome and was reported to have been powered to detect a three unit difference in hot flush scores between groups. The Panel notes that the studies by Knight et al. (2001) and St. Germain et al. (2001) might have been underpowered to detect a statistically significant effect of soy isoflavones on the severity of hot flushes.

None of the three RCTs (Cheng et al., 2007; St Germain et al., 2001; Upmalis et al., 2000) investigating the effect of soy isoflavones on frequency or severity of night sweats reported a statistically significant difference between groups. Although both frequency and severity of night sweats were assessed in the study by Cheng et al. (2007), results for severity of night sweats only were reported in the paper.

The Panel notes that the human intervention studies provided are inconsistent with respect to an effect of soy isoflavones on frequency and/or severity of hot flushes, and that none of the RCTs which investigated night sweats showed an effect on night sweats.

With regard to the mechanism by which soy isoflavones could exert the claimed effect, it has been proposed that soy isoflavones could have a weak oestrogenic effect on ERβ. This was investigated in the three *in vitro* studies (Choi et al., 2008; Harris et al., 2005; Kuiper et al., 1997) provided, which assessed the affinity of isoflavones to ERα and ERβ and their half maximal inhibitory concentration (IC_{50}) and their half maximal effective concentration (EC_{50}), and reported that isoflavones had a greater potency to bind to ERβ than to ERα *in vitro*.

It was proposed in the information provided that ERβ could play a role in body temperature control through which soy isoflavones could be involved in the regulation of vasomotor stability.

The Panel notes that currently there is no consensus on the physiological pathways involved in the occurrence of hot flushes (Andrikoula and Prelevic, 2009; Stearns et al., 2002), and considers that the evidence provided for a possible mechanism by which soy isoflavones could exert an effect on vasomotor symptoms is weak.

In weighing the evidence, the Panel took into account that the evidence provided by 15 human intervention studies is inconsistent with respect to an effect of soy isoflavones on reduction of vasomotor symptoms. The Panel also took into account that most of these studies were at high risk of bias, that the inconsistent results could not be explained by dose, sample size, study duration, or baseline frequency or severity of vasomotor symptoms, and that the evidence of the proposed mechanism of action is weak.

The Panel concludes that the evidence provided is insufficient to establish a cause and effect relationship between the consumption of soy isoflavones and reduction of vasomotor symptoms associated with menopause.

CONCLUSIONS

On the basis of the data presented, the Panel concludes that:

- The food constituent, soy isoflavones, which is the subject of the health claims, is sufficiently characterised.

Maintenance of bone mineral density (ID 1655)

- The claimed effect which is eligible for further assessment relates to the maintenance of bone mineral density. The proposed target population is post-menopausal women. Maintenance of bone mineral density is a beneficial physiological effect.
- The evidence provided is insufficient to establish a cause and effect relationship between the consumption of soy isoflavones and maintenance of bone mineral density in post-menopausal women.

Reduction of vasomotor symptoms associated with menopause (ID 1654, 1704, 2140, 3093, 3154, 3590)

- The claimed effect which is eligible for further assessment relates to the reduction of vasomotor symptoms associated with menopause. The proposed target population is peri- and post-menopausal women. Reduction of vasomotor symptoms associated with menopause is a beneficial physiological effect.
- The evidence provided is insufficient to establish a cause and effect relationship between the consumption of soy isoflavones and reduction of vasomotor symptoms associated with menopause.

DOCUMENTATION PROVIDED TO EFSA

Health claims pursuant to Article 13 of Regulation (EC) No 1924/2006 for further assessment (No: EFSA-Q-2012-00165, EFSA-Q-2012-00166, EFSA-Q-2012-00167, EFSA-Q-2012-00170, EFSA-Q-2012-00212, EFSA-Q-2012-00213, EFSA-Q-2012-00214). The scientific substantiation is based on the information provided by the Member States in the consolidated list of Article 13 health claims, references that EFSA has received from Member States or directly from stakeholders and the additional information provided by the competent Authorities of Germany and Austria for further assessment of this claim (available at: http://www.efsa.europa.eu/en/topics/topic/article13.htm).

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APPENDICES

APPENDIX A

BACKGROUND AND TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION

The Regulation 1924/2006 on nutrition and health claims made on foods[6] (hereinafter "the Regulation") entered into force on 19th January 2007.

Article 13 of the Regulation foresees that the Commission shall adopt a Community list of permitted health claims other than those referring to the reduction of disease risk and to children's development and health. This Community list shall be adopted through the Regulatory Committee procedure and following consultation of the European Food Safety Authority (EFSA).

Health claims are defined as "any claim that states, suggests or implies that a relationship exists between a food category, a food or one of its constituents and health".

In accordance with Article 13 (1) health claims other than those referring to the reduction of disease risk and to children's development and health are health claims describing or referring to:

a) the role of a nutrient or other substance in growth, development and the functions of the body; or
b) psychological and behavioural functions; or
c) without prejudice to Directive 96/8/EC, slimming or weight-control or a reduction in the sense of hunger or an increase in the sense of satiety or to the reduction of the available energy from the diet.

To be included in the Community list of permitted health claims, the claims shall be:

(i) based on generally accepted scientific evidence; and
(ii) well understood by the average consumer.

Member States provided the Commission with lists of claims as referred to in Article 13 (1) by 31 January 2008 accompanied by the conditions applying to them and by references to the relevant scientific justification. These lists have been consolidated into the list which forms the basis for the EFSA consultation in accordance with Article 13 (3).

ISSUES THAT NEED TO BE CONSIDERED

IMPORTANCE AND PERTINENCE OF THE FOOD[7]

Foods are commonly involved in many different functions[8] of the body, and for one single food many health claims may therefore be scientifically true. Therefore, the relative importance of food e.g. nutrients in relation to other nutrients for the expressed beneficial effect should be considered: for functions affected by a large number of dietary factors it should be considered whether a reference to a single food is scientifically pertinent.

It should also be considered if the information on the characteristics of the food contains aspects pertinent to the beneficial effect.

SUBSTANTIATION OF CLAIMS BY GENERALLY ACCEPTABLE SCIENTIFIC EVIDENCE

[6] OJ L12, 18/01/2007
[7] The term 'food' when used in this Terms of Reference refers to a food constituent, the food or the food category.
[8] The term 'function' when used in this Terms of Reference refers to health claims in Article 13(1)(a), (b) and (c).

Scientific substantiation is the main aspect to be taken into account to authorise health claims. Claims should be scientifically substantiated by taking into account the totality of the available scientific data, and by weighing the evidence, and shall demonstrate the extent to which:

(a) the claimed effect of the food is beneficial for human health,

(b) a cause and effect relationship is established between consumption of the food and the claimed effect in humans (such as: the strength, consistency, specificity, dose-response, and biological plausibility of the relationship),

(c) the quantity of the food and pattern of consumption required to obtain the claimed effect could reasonably be achieved as part of a balanced diet,

(d) the specific study group(s) in which the evidence was obtained is representative of the target population for which the claim is intended.

EFSA has mentioned in its scientific and technical guidance for the preparation and presentation of the application for authorisation of health claims consistent criteria for the potential sources of scientific data. Such sources may not be available for all health claims. Nevertheless it will be relevant and important that EFSA comments on the availability and quality of such data in order to allow the regulator to judge and make a risk management decision about the acceptability of health claims included in the submitted list.

The scientific evidence about the role of a food on a nutritional or physiological function is not enough to justify the claim. The beneficial effect of the dietary intake has also to be demonstrated. Moreover, the beneficial effect should be significant i.e. satisfactorily demonstrate to beneficially affect identified functions in the body in a way which is relevant to health. Although an appreciation of the beneficial effect in relation to the nutritional status of the European population may be of interest, the presence or absence of the actual need for a nutrient or other substance with nutritional or physiological effect for that population should not, however, condition such considerations.

Different types of effects can be claimed. Claims referring to the maintenance of a function may be distinct from claims referring to the improvement of a function. EFSA may wish to comment whether such different claims comply with the criteria laid down in the Regulation.

WORDING OF HEALTH CLAIMS

Scientific substantiation of health claims is the main aspect on which EFSA's opinion is requested. However, the wording of health claims should also be commented by EFSA in its opinion.

There is potentially a plethora of expressions that may be used to convey the relationship between the food and the function. This may be due to commercial practices, consumer perception and linguistic or cultural differences across the EU. Nevertheless, the wording used to make health claims should be truthful, clear, reliable and useful to the consumer in choosing a healthy diet.

In addition to fulfilling the general principles and conditions of the Regulation laid down in Article 3 and 5, Article 13(1)(a) stipulates that health claims shall describe or refer to "the role of a nutrient or other substance in growth, development and the functions of the body". Therefore, the requirement to describe or refer to the 'role' of a nutrient or substance in growth, development and the functions of the body should be carefully considered.

The specificity of the wording is very important. Health claims such as "Substance X supports the function of the joints" may not sufficiently do so, whereas a claim such as "Substance X helps maintain the flexibility of the joints" would. In the first example of a claim it is unclear which of the various functions of the joints is described or referred to contrary to the latter example which specifies this by using the word "flexibility".

The clarity of the wording is very important. The guiding principle should be that the description or reference to the role of the nutrient or other substance shall be clear and unambiguous and therefore be specified to the extent possible i.e. descriptive words/ terms which can have multiple meanings should be avoided. To this end, wordings like "strengthens your natural defences" or "contain antioxidants" should be considered as well as "may" or "might" as opposed to words like "contributes", "aids" or "helps".

In addition, for functions affected by a large number of dietary factors it should be considered whether wordings such as "indispensable", "necessary", "essential" and "important" reflects the strength of the scientific evidence.

Similar alternative wordings as mentioned above are used for claims relating to different relationships between the various foods and health. It is not the intention of the regulator to adopt a detailed and rigid list of claims where all possible wordings for the different claims are approved. Therefore, it is not required that EFSA comments on each individual wording for each claim unless the wording is strictly pertinent to a specific claim. It would be appreciated though that EFSA may consider and comment generally on such elements relating to wording to ensure the compliance with the criteria laid down in the Regulation.

In doing so the explanation provided for in recital 16 of the Regulation on the notion of the average consumer should be recalled. In addition, such assessment should take into account the particular perspective and/or knowledge in the target group of the claim, if such is indicated or implied.

TERMS OF REFERENCE

HEALTH CLAIMS OTHER THAN THOSE REFERRING TO THE REDUCTION OF DISEASE RISK AND TO CHILDREN'S DEVELOPMENT AND HEALTH

EFSA should in particular consider, and provide advice on the following aspects:

- Whether adequate information is provided on the characteristics of the food pertinent to the beneficial effect.
- Whether the beneficial effect of the food on the function is substantiated by generally accepted scientific evidence by taking into account the totality of the available scientific data, and by weighing the evidence. In this context EFSA is invited to comment on the nature and quality of the totality of the evidence provided according to consistent criteria.
- The specific importance of the food for the claimed effect. For functions affected by a large number of dietary factors whether a reference to a single food is scientifically pertinent.

In addition, EFSA should consider the claimed effect on the function, and provide advice on the extent to which:

- the claimed effect of the food in the identified function is beneficial.
- a cause and effect relationship has been established between consumption of the food and the claimed effect in humans and whether the magnitude of the effect is related to the quantity consumed.
- where appropriate, the effect on the function is significant in relation to the quantity of the food proposed to be consumed and if this quantity could reasonably be consumed as part of a balanced diet.
- the specific study group(s) in which the evidence was obtained is representative of the target population for which the claim is intended.
- the wordings used to express the claimed effect reflect the scientific evidence and complies with the criteria laid down in the Regulation.

When considering these elements EFSA should also provide advice, when appropriate:

- on the appropriate application of Article 10 (2) (c) and (d) in the Regulation, which provides for additional labelling requirements addressed to persons who should avoid using the food; and/or warnings for products that are likely to present a health risk if consumed to excess.

APPENDIX B

EFSA DISCLAIMER

The present opinion does not constitute, and cannot be construed as, an authorisation to the marketing of the food/food constituent, a positive assessment of its safety, nor a decision on whether the food/food constituent is, or is not, classified as foodstuffs. It should be noted that such an assessment is not foreseen in the framework of Regulation (EC) No 1924/2006.

It should also be highlighted that the scope, the proposed wordings of the claims and the conditions of use as proposed in the Consolidated List may be subject to changes, pending the outcome of the authorisation procedure foreseen in Article 13(3) of Regulation (EC) No 1924/2006.

GLOSSARY AND ABBREVIATIONS

ANCOVA	Analysis of covariance
B-ALP	Bone alkaline phosphatase
BMC	Bone mineral content
BMD	Bone mineral density
CTx	cross-linked C-telopeptides of type 1 collagen
DPYR	Deoxypyridinoline cross-links
DXA	Dual-energy x-ray absorptiometry
EC_{50}	Half maximal effective concentration
ER	Oestrogen receptor
HRT	Hormone replacement therapy
IC_{50}	Half maximal inhibitory concentration
ITT	Intention-to-treat
LOCF	Last observation carried forward
MITT	Modified intention-to-treat
NTx	cross-linked N-telopeptides of type 1 collagen
PP	Per protocol
PYR	Pyridinoline cross-links
RCT	Randomised controlled trial
SERM	Selective oestrogen receptor modulators